Appendix F

F.1 Dermal Uptake of Chemicals from Soil

F.1.1. Introduction

The internal dose experienced during a dermal exposure to soil-bound chemicals depends on many factors. An algorithm that describes the uptake of chemicals from soil as a function of exposure duration, exposure frequency, chemical concentration in the soil, soil loading, surface area, body weight, averaging time, and fractional absorption (ABS) is discussed in Chapter 6. The purpose of section F.1 is to summarize ABS for selected chemicals. The chemicals are 4,4'-methylene dianiline, hexachlorocyclohexanes, diethylhexylphthalate, polychlorinated dibenzodioxins and dibenzofurans as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), pentachlorophenol, polycyclic aromatic hydrocarbons (PAHs) as benzo[a]pyrene (BaP), and the salts of arsenic, beryllium, cadmium, mercury, lead, nickel, and chromium (specifically hexavalent chromium). The chemicals are on a list of "Hot Spots" substances, and the basis for their selection for ABS can be found in Appendix E. To familiarize the reader with some of the complex issues of dermal absorption of chemicals from soil, a general discussion is presented before the summaries of the selected chemicals.

An ABS is a chemical-dependent, scenario-dependent value that can vary with the characteristics of the soil matrix and the exposed population. Such characteristics include the relative lipophilicity/hydrophilicity of the compound, soil organic content, soil particle size, age of the exposed receptor, residence time on the skin, exposed surface area. Some of these issues are discussed in Chapter 6. Ideally, a mathematical distribution that takes into account the variabilities of these characteristics, should be used to determine what ABS value is used in a given scenario. Sufficient information, however, does not exist for such a procedure. Hence, the ABS values derived in this document are point estimates. Where sufficient data are not available for the derivation of a point estimate ABS, a default ABS is recommended.

The uptake of chemicals across skin involves a complex process of transport from the soil matrix to the external protective skin layer called the stratum corneum, and through the stratum corneum to the underlying skin tissue. Within the dermis are located networks of blood vessels, nerves, and lymphatics. During the transport through the viable-epidermal and dermal layers, metabolism also plays a role (Kao and Carver, 1990). Ultimately the absorbed chemical enters the systemic circulation and becomes available to the tissues. Specific dermal ABSs from soil-bound chemicals are difficult to obtain due in part to the complex multiphasic nature of the system. Hawley (1985) suggested a default factor of 15 percent to correct for the effect of the soil matrix on the dermal uptake of organic chemicals. Experimental evidence, however, suggests absorption from soil will be chemical dependent (see following sections). Hence, it is important to determine dermal uptake values for specific soil-bound chemicals where appropriate data are available, as they will be more accurate than those derived on broad-based assumptions.

To obtain the ABS, a measured amount of chemical in a given amount of soil is administered to the skin surface, and this amount (wgt chemical/area skin) is referred to as the applied dose. The amount of chemical that crosses the skin barrier is measured and the ABS is calculated by dividing the amount absorbed by the amount applied. (When measurements are made on excreta or specific organs, corrections are included for incomplete recovery.). In experiments of this type, the administered amount (in soil or solvent) represents a finite level of application. The ABS so calculated is an experimental value, measured under a specific set of exposure conditions, and will vary as the experimental conditions vary.

In contrast to the studies that utilize the application of finite amounts of chemicals, dermal studies that mimic scenarios such as bathing and swimming, require the applications of infinite volumes, i.e. the volume of the administered dose is much larger than the volume of the exposed skin area and the chemical at the skin surface is continuously replenished. The latter exposure scenario is not applicable to the soil studies described in this chapter, although information obtained from such studies may be useful for discussion purposes. For additional information on dermal uptake of chemicals from water (or vapor), the reader is referred to USEPA (1992, chapters 5 and 7).

F.1.2 Risk Assessment Issues

Although all studies are useful for understanding the relationship between dermal exposure and absorption, the application of these studies to risk assessment, in particular the uptake of soil-bound chemicals involves specific issues that need clarification. Included among these issues are biological characteristics, soil properties, and exposure scenarios, and the variability in each can introduce uncertainties into the point estimate determination of ABS. By understanding these issues, the implications of using experimentally derived dermal ABS can be better understood. The use of such information, however, is qualitative, not quantitative. Specific categories of issues that need clarification when assessing dermal absorption are discussed below.

F.1.2.1 Definitions of soil content

Because different authors use different terms to represent the level of chemical and the level of soil, the following definitions will be used (See Glossary): soil loading = weight of soil/area skin; applied dose = weight chemical/area skin; chemical content of soil = weight of chemical/weight of soil.

F.1.2.2 Definition of dermal uptake

Dermal uptake may be defined as the amount of chemical crossing the outer skin layer (stratum corneum) into the underlying skin tissue regardless of its disposition, or the amount that becomes systemically available. Ideally, the measure of dermal uptake is the amount of chemical absorbed at the site of application (after the unabsorbed amount has been removed), plus the amount in the tissues, carcass, and excreta. Among the studies cited, no consistent experimental protocol was used. Among the inorganic chemicals, some measurements were carried out on skin tissue only, while others relied on urinary

excretion. For the organic compounds, the measure of uptake was the content in the excreta and/or tissues. Hence the reader should be aware that the recommended ABS values represent different experimental protocols.

An important component of dermal absorption is the retention (i.e., not readily washed off) of the chemical at the site of application. Such retention may provide a reservoir for future systemic absorption. For example, Wester, et al. (1990) reported an incomplete recovery of soil-bound BaP from the site of application after a soap/water wash. Banks and Birnbaum (1991) observed the apparent migration of TCDD (from acetone) from the stratum corneum into the viable epidermis after 1-5 day's exposure.

F.1.2.3 Soil contamination history

The absorption of soil-bound chemicals may be affected by the history of the contamination episode. TCDD that contaminated soil during surface spraying with contaminated oil was more bioavailable than TCDD bound to soil during a long period of accumulation from leakage from a manufacturing plant (Umbreit, et al., 1988). In contrast, the bioavailabilities of TCDD in two soils, each contaminated during surface spraying, were similar (McConnell, et al., 1984). Even within the same contamination episode, more than one pool of contaminant-laden soil may exist. For example, TCDD-contaminated Seveso soil contained two pools of TCDD, one with a half life of 23 days and another with a half-life of 9 years (Bertazzi and de Domenico, 1994).

F.1.2.4 Soil loading

The ABS from soil depends on the amount of soil in contact with the skin, and the role of soil loading in dermal uptake is discussed in some detail in the previous section. Theoretical calculations and experimental data show increased soil loading (mg soil/cm^2 skin) leads to decreased fractional absorption (McKone, 1990; Howd and McKone, 1991; Duff and Kissel, 1996). Maximal absorption of a soil-bound chemical occurs when a monolayer of soil covers the skin (monolayer threshold), and the soil loading at which the monolayer exists depends on the soil particle size (Duff and Kissel, 1996). Many experiments are carried out under conditions of high soil loading, e.g. 20 - 40 mg/cm^2 (see e.g. Shu, et al., 1988; Wester, et al., 1990, 1992a, 1993a,b), whereas typical loadings under most human exposure scenarios are considered by USEPA (1992) to be between 0.2 and 1.0 mg/cm^2. Although USEPA (1992) suggests a procedure to correct the high soil loads to those encountered under more routine exposures, the correction does not take into account particle size or the presence of rate-limiting diffusion. In the studies described in this chapter, insufficient information is available with which to make extrapolations to a predetermined soil load. The reader should be aware, however, that soil loading, particle size, and diffusion can affect the ABS value.

F.1.2.5 Soil condition

For experimental purposes, the soil used to measure dermal uptake, is applied to the skin as a "dry" formulation, i.e. the solvent used in the preparation of the chemical laden soil, is allowed to evaporate prior to dermal application. The uptake of a soil-

bound chemical from wet soil is expected to exceed the uptake from dry soil because of the increased humidity and temperature at the skin surface (Wester and Maibach, 1983). Such conditions exist for human exposure scenarios that involve high humidity, high temperature, and skin covering (e.g. gloves and clothing). Each condition may affect the uptake in a different manner and a direct extrapolation from the "dry" formulation of the laboratory to the "environmental" formulation, is not possible. However, some studies are carried out under condition of occluded skin, and these studies could be used to estimate chemical absorption from soil when moisture is present.

F.1.2.6 In Vivo Vs. In Vitro Experiments

In vitro studies have the advantage of measuring dermal absorption under controlled environments, and diffusion cells, organ cultures and isolated skin flaps have been used to study the dermal uptake of chemicals (Wester and Maibach, 1983; Kao and Carver, 1990; Brooks and Riviere, 1996). Diffusion cell studies have been the source of the *in vitro* data used to estimate dermal uptake, but the extent of uptake is low compared to that measured *in vivo* (Ng, et al., 1992; Wester, et al., 1993a,b). The sources for the difference have not been established and could include changes in properties such as hydration and altered metabolism that contribute to the total absorption of some chemicals across the skin. Excluded from the artificial *in vitro* diffusion cell systems, are the capillary membranes and blood flow that provide a more efficient mechanism for removing material absorbed across the skin. Another *in vitro* experimental approach to studying dermal absorption is the use of isolated skin flaps that maintain the skin microvasculature (Kao and Carver, 1990). This system, however, has not been applied to the determination of ABS values. The considerations discussed above suggest that for exposure assessment purposes, *in vivo* data are preferable to the available *in vitro* data.

F.1.2.7 Species Specificity

The data of Wester and Maibach (1975 and 1983) suggest that the extent of *in vivo* uptake among animals follows the rank: rabbit > rat > pig ≈ monkey ≈ humans. The conclusion is based on the combined data from studies with benzoic acid, hydrocortisone, testosterone, caffeine, N-acetylcysteine, and butter yellow. This rank has sometimes been used to decrease estimates of potential human dermal uptake when data are obtained from the commonly used experimental animal, rat. Factors that could affect this conclusion are the chemical specificity of the species dependence and the anatomical site of application. The species dependence is not known for all chemicals. Inspection of the graph presented in Wester and Maibach (1983) suggest extreme differences between species are not always constant across all chemicals. For example, the absorption of haloprogin is much greater in rabbit than in pig, whereas for butter yellow absorption by rabbit and pig are similar. For caffeine, the absorption by rat and human are similar, whereas for testosterone, greater absorption occurs in rat. Wester and Maibach (1983) also report the rank for absorption of lindane and parathion was reversed for squirrel monkey and pig. Among humans some skin areas of the body are more efficient absorbers than the commonly used forearm (e.g. scalp, axilla, forehead, jaw angle and

scrotum) (Maibach et al., 1971). Caution should therefore be exercised when concluding that dermal ABSs obtained from rat and rabbit are *a priori* greater than those for humans.

F.1.2.8 Soil - Chemical - Tissue Interaction.

In the absence of total disposition analyses, the extent of systemic dermal absorption is based on the recovery of the chemical (and metabolites) in the excreta or in an organ. The data are then corrected for incomplete recovery by measuring the chemical (and metabolites) following intravenous (iv), intramuscular (im), or oral (po) administration. The iv, im, or po uptake measurements, however, are based on the chemical dissolved in solvent and not mixed in soil. The effect of soil on the uptake of chemicals by any route of administration is not known *a priori*. Polychlorinated biphenyls and arsenic are absorbed across the skin similarly from soil and solvent (Wester, et al. 1993a,b), whereas Cd (Wester, et al., 1992a), BaP and 1,1,1-trichloro-2,2-bis (4-chlorophenyl)ethane (Wester, et al., 1990) are absorbed to a smaller extent from soil than from solvent vehicle. TCDD absorption, as measured by TCDD content of the liver following gavage, is decreased by 34 percent in the presence of soil (Poiger and Schlatter, 1980). The use of solvent dissolved chemicals to correct for dermal absorption of soil-bound chemicals could lead to errors, but insufficient data are available to determine the extent of the error for all chemicals or for dermal absorption specifically.

F.1.2.9 Frequency/Duration Time

Published dermal uptake data are usually based on short-term exposure scenarios that do not address the effect of long term or repeated exposures. Such exposures could take place in dusty environments, among humans that do not have access to daily washing facilities (homeless people, military personnel), and children whose play activities render them more accessible to repeated soil contamination. Fenske and Lu (1994) found that the fraction of washable organophosphate on the hands decreased after 1 hour residence time. Other studies on the effect of exposure duration and/or frequency on the dermal uptake of chemicals used solvent vehicles. Dermal uptake of solvent-dissolved TCDD and two -furan congeners under conditions of repeated low-dose, chronic exposures (two times per week for twenty weeks), demonstrated the toxicity associated with each congener increased with increasing exposure frequency and/or exposure duration (Hebert, et al., 1990). The results described by Hebert, et al. (1990) could be due to increased exposure frequency and/or increased exposure duration. Wester, et al. (1977) show that for hydrocortisone, repeated dermal application to Rhesus monkey under acute exposure conditions, did not lead to increased uptake. Although the hydrocortisone data suggest the effects observed in the Hebert, et al. (1990) study may be due only to increased exposure duration, chemical specific data are needed. In the case of a one-time dermal exposure, TCDD apparently migrated from the stratum corneum into the viable epidermis after exposure for 1-5 days (Banks and Birnbaum, 1991).

F.1.2.10 Metabolism and Toxicokinetics

The description of percutaneous absorption is generally based on diffusion models that take into account the physico-chemical characteristics of chemicals and soils (see e.g. McKone, 1990). While such descriptions may help to explain the uptake of chemicals across the stratum corneum, the role played by metabolism in the viable epidermal and dermal layers should be included to understand the complete permeation of chemicals through the skin (Wester and Maibach, 1983; Kao and Carver, 1990; Bronaugh, et al., 1994). *In vivo* dermal uptake measurements rely on tissue or excreta content and will reflect the total process from uptake at the skin surface to systemic distribution and elimination. Isolated preparations of stratum cornea could be used to study the uptake of chemicals by the skin surface, but these studies do not reflect the *in vivo* situation. Although enzymes responsible for the metabolism of organic chemicals have been detected in skin preparations, (Kao and Carver, 1990), the role played by the skin enzymes in the systemic absorption of organic chemicals in not understood. In one case, however, the formation of polycyclic aromatic hydrocarbon (PAH)-DNA adducts in the skin following dermal application of PAH-containing mixtures was reported (Philips, et al., 1990).

Non-metabolized chemicals may remain in one or more skin layers. TCDD, found in the stratum corneum immediately after dermal exposure, migrated into the viable epidermis after 1-5 days (Banks and Birnbaum, 1991). Based on free metabolite content, the dermal metabolism of BaP, *in vitro*, was determined to be minimal (Storm, et al., 1990; Wester, et al., 1990), but the BaP was not completely removed from the site of application with soap/water washes (Wester, et al., 1990). The BaP remaining in the skin could be in the form of the parent compound or DNA-adducts. The latter were observed by Philips, et al. (1990) in their study on dermal uptake of PAHs from crude mixtures.

F.1.2.11 Experimental vs. Real-life Exposure Scenarios/Sensitive Populations

To interpret experimental results, studies are designed to ensure uniformity within the experimental population. The human population, however, is not uniform, and dermal uptake may vary with changes in characteristics such as **age**. Using TCDD or 2,3,4,7,8-pentachlorodibenzo-p-dioxin (4-PeCDD) in solvent, Banks, et al. (1990) observed greater absorption of TCDD or 4-PeCDD in 10-week old rats than rats of 36 - 120-weeks of age. Wester and Maibach (1983) suggest the skin of young animals, including preterm infants, may be more sensitive than adults to dermal penetration because of an incompletely developed dermal barrier function. The increased surface area to body weight ratio among the very young, will lead to a greater systemic dose. Although the surface area to body weight ratio may be controlled experimentally, under most human exposure scenarios, such control will not exist.

Controlled studies on dermal absorption are performed under conditions where the skin exists in a healthy, undamaged state. Under conditions where skin damage may occur, dermal absorption of chemicals may increase. The chemical may itself contribute

to skin damage, as Roberts, et al. (1977) observed for some phenols in an *in vitro* study. In addition to chemical related skin irritation, some work activities may add to the damage, e.g. stacking chlorophenol treated lumber (Fenske, et al., 1987) or picking fruit from trees treated with paraquat (Newhouse, et al., 1978).

A major distinction between the experimental studies used to determine dermal uptake of individual chemicals and ordinary human exposure scenarios, is the presence of the soil-bound chemical as a component of a mixture of chemicals in the human scenario. The presence of such mixtures is evident from the dioxin/dibenzofuran data obtained from the ashes associated with metal recovery facilities, open burn sites, and a railroad car incineration facility in California (Harnly, et al., 1995). The potential interaction among the components of the mixture cannot be determined *a priori*. For example, the dermal uptake of TCDD was similar from laboratory prepared TCDD soil (100 ppb) and from soil that had been environmentally contaminated with TCDD-containing oil (123 ppb) (Shu, et al., 1988). For BaP, however the dermal retention half-life was increased in the presence of various coal-derived fractions (Dankovic, et al., 1989). Many chemicals are inducers of skin enzyme activities (Kao and Carver, 1990) and exposure to these inducers could affect the total systemic absorption of other chemicals. Clearly, more research data are needed to address the effect of chemicals in mixtures on dermal uptake.

F.1.3 Point Estimates For Dermal Uptake Of Selected Inorganics

F.1.3.1 Arsenic

Recommended point estimate for dermal uptake: 4% (based on Wester *et al.*, 1993b)

F.1.3.1.1 Studies Considered

A. Key Study

Wester *et al.* (1993b) examined the percutaneous absorption of arsenic-73 (^{73}As) as H_3AsO_4 from soil, both *in vivo* and *in vitro*. The *in vivo* study was conducted in female Rhesus monkeys (n = 4 animals per dose group). Two dose levels were used: 0.0004 and 0.6 μg/cm^2 (micrograms of arsenic per cm^2 skin surface exposed). The soil load on the skin was 0.04 g soil/cm^2 skin area. Topical doses were applied to an area of the abdomen for 24 hours. Urine was collected during the dosing period, and through the following 6 days. For comparison, 3 μCi ^{73}As in water was administered intravenously to four monkeys. Percutaneous absorption was determined by the ratio of urinary arsenic excretion following topical application to that following intravenous administration. Results of this study showed that the percutaneous absorption of arsenic from soil was 4.5 ± 3.2% from the low dose and 3.2 ± 1.9% from the high dose (nonsignificant difference).

The *in vitro* study (Wester *et al.*, 1993b) was conducted using human cadaver skin from three separate donor sources with three replicates from each source. Only the low dose was tested (0.0004 μg arsenic per cm^2 skin surface exposed.) The soil load on the

skin samples was 0.04 g soil per cm^2 skin area, and phosphate-buffered saline served as receptor fluid. The *in vitro* exposure period was 24 hours. Percutaneous absorption through human cadaver skin was 0.8%, calculated as receptor fluid accumulation plus residual skin concentration (after soap and water wash).

B. Other Studies

Dutkiewicz (1977) immersed rat tails in 0.01-0.2 M aqueous solutions of sodium arsenate (containing ^{74}As) for 1 hour. The rate of arsenic uptake was reported as a range, 1-33 $\mu g/cm^2$-hr. Data were not provided to allow estimation of the total amount absorbed at a given concentration.

F.1.3.1.2 Selection of Absorption Value

A. Discussion

Wester *et al.* (1993b) was the only available soil study that provided quantitative data on dermal absorption. The paper contains data from both *in vivo* and *in vitro* experiments, as summarized above. While the *in vitro* study was conducted with human skin samples, the *in vivo* Rhesus monkey data have been selected as providing a better estimate of absorption for the general human population. *In vitro* studies do have the advantage of allowing the use of human skin and controlled environments; however, *in vitro* experiments may not accurately mimic metabolic processes of living systems (Wester and Maibach, 1983; USEPA, 1992; Schaum, 1993).

The percutaneous absorption of arsenic from soil ranged from 3-5% in the *in vivo* experiment by Wester *et al*. (1993b). The most health-conservative approach would be to select the highest value from the range as the default point estimate. Due to the nonsignificant difference in the absorption values between the two dose groups, it is also appropriate to calculate the arithmetic mean, 4%, as the default point estimate for arsenic for this exposure pathway.

B. Other Agencies' Default Values

Currently, California's Department of Toxic Substances Control (DTSC) and USEPA's Region IX both recommend using 3% based on the *in vivo* data in Wester *et al.*, 1993b (Cal/EPA, 1994; USEPA, 1995b).

C. Recommendation

OEHHA recommends adopting 4% as the default point estimate for dermal uptake of arsenic.

F.1.3.2 Beryllium

Recommended point estimate for dermal uptake: 1.0% (Clement Associates, 1988)

F.1.3.2.1 Studies Considered

No quantitative data on percutaneous absorption of beryllium were located.

Belman (1969) investigated the interaction of beryllium with guinea pig epidermal tissue in order to explore a mechanism for the delayed allergic skin reaction observed in humans following beryllium exposure. Using both *in vitro* and *in vivo* experiments, he reported that beryllium is taken up into the skin and localized primarily in the epidermis where it binds to proteins, causes a localized immune response and results in rapid destruction of skin cells. Data are not provided, however, regarding the amount of beryllium taken up by the skin cells, or the fate of beryllium following the immunological response (i.e., whether beryllium is then absorbed into circulation, or sloughed off with cells.)

Petzow and Zorn (1974) reported on the absorption of beryllium through the tail skin of rats exposed to an aqueous beryllium chloride solution spiked with ^{7}Be. The authors stated that within the first hour of exposure there is an increase in the rate of beryllium uptake. After approximately 90 minutes, the dermal flux of beryllium from the aqueous solution is constant. In addition, Petzow and Zorn reported that the amount of beryllium that diffuses through the skin seems to be dependent upon the concentration of beryllium in contact with the skin.

F.1.3.2.2 Selection of Absorption Value

A. Discussion

Due to the lack of quantitative data regarding dermal absorption of beryllium, it is not possible to calculate a chemical-specific value at this time.

The South Coast Air Quality Management District's Multi-Pathway Health Risk Assessment Input Parameters Guidance Document (Clement Associates, 1988) recommends using a default value of 1% for inorganic chemicals when quantitative data are not available to estimate chemical-specific dermal absorption fractions from soil. The CAPCOA Air Toxics "Hot Spots" Program Revised 1992 Risk Assessment Guidelines (CAPCOA, 1993) recommends using these same numbers based on the Clement (1988) report. In addition, Cal/EPA's Department of Toxic Substances Control (Cal/EPA, 1994), as well as USEPA's Region IX (USEPA, 1995b) recommend use of the Clement (1988) default values.

In 1993, USEPA staff (Schaum and Hoang, 1993) reviewed Cal/EPA dermal absorption fractions from soil, and in doing so, provided the following comments on the Clement Associates (1988) report:

> "Using data available prior to 1988, this document recommends default values for absorption of chemicals from soil: 1% for inorganics, 10% for organics. The applicability of the pre-1988 data is questionable since it

included so few experiments using soil. Furthermore, we are uncomfortable with the assumption that the limited test data represent such broad classes of compounds. If this assumption is valid, then the default values are in the right order of magnitude (1% for inorganics compared to 0.1% for cadmium, 3% for arsenic, 10% for organics compared to 0.1% - 25% for available data)."

OEHHA staff agree with USEPA's 1993 comments.

B. Other Agencies' Default Values

As discussed above, USEPA's Region IX, Cal/EPA's Department of Toxic Substances Control, and CAPCOA currently recommend 1% as the default dermal absorption value for beryllium, based on the Clement Associates (1988) document.

C. Recommendation

Until further data are available (data on beryllium allowing determination of a chemical-specific number, or data on other inorganics suggesting a more appropriate default value for metals in general), OEHHA recommends adopting 1% as the default point estimate for dermal uptake of beryllium. This value is consistent with Cal/EPA's DTSC and USEPA Region IX.

F.1.3.3 Cadmium

Recommended point estimate for dermal uptake: 0.1% (based on Wester *et al.*, 1992a)

F.1.3.3.1 Studies Considered

A. Key Study

Wester *et al.* (1992a) examined the percutaneous absorption of cadmium chloride from soil using human cadaver skin in an *in vitro* system. Human plasma was used as the receptor fluid. Radiolabeled cadmium (^{109}Cd) was mixed with soil at a concentration of 13 ppb. The soil load on the skin samples was 0.02 g/cm^2 (gram soil per square centimeter skin exposed) or 0.04 g/cm^2. Two donor skin sources were used with replicates for each of the soil concentrations. At the end of a 16-hour exposure, soil was removed from the samples by soap and water rinse. Percutaneous absorption, calculated as receptor fluid accumulation plus residual skin concentration after soap and water wash, ranged from 0.08% to 0.2% of applied dose. No significant differences were observed in absorption between skin samples or soil load concentrations. The data are presented in the table below.

Table 6.12 In Vitro Percutaneous Absorption of Cadmium from Soil (from Wester et al., 1992a)

		Percentage Applied Dose		
	Skin Source	Receptor Fluid	Skin	Total
Soil 0.04 g/cm^2	1	0.02 ± 0.01	0.06 ± 0.02	0.08
	2	0.07 ± 0.03	0.13 ± 0.05	0.20
Soil 0.02 g/cm^2	3	0.02 ± 0.02	0.08 ± 0.06	0.1
	4	0.02 ± 0.02	0.08 ± 0.06	0.1

Note: n = 3 replicates per skin source

B. Other Studies

Kimura and Otaki (1972) used liver and kidney accumulation of cadmium in rabbits and hairless mice to estimate dermal absorption. A total dose of 30.5 mg Cd (in an aqueous $CdCl_2$ solution) was administered to rabbit skin (n=1) in 5 doses over 3 weeks. Two weeks after the final application, 0.40% of the applied dose was found in liver and kidney combined. In rabbits (n=2) administered a total dose of 61 mg Cd in multiple ointment applications, 0.45 and 0.61% of the applied doses were found in liver and kidney combined. Dermal absorption of cadmium in hairless mice, estimated from kidney and liver accumulation, ranged from 0.07-0.27% after a single application of ointment (0.61 mg Cd). Cadmium absorption after multiple ointment applications on hairless mice ranged from 0.59 - 0.87% of applied dose.

F.1.3.3.2 Selection of Absorption Value

A. Discussion

Wester *et al.* (1992a) was the only study that provided quantitative data on dermal absorption of cadmium from soil. The mean percentage of cadmium absorbed from all twelve samples (2 soil concentrations x 2 skin sources per soil concentration x 3 replicates) was 0.1%.

B. Other Agencies' Default Values

U.S. EPA (1992) recommends a range of 0.1 to 1.0% for exposure assessments based on Wester *et al.* (1992a). USEPA Region IX recommends 0.1% to be used as part of their Preliminary Remediation Goals, and California's Department of Toxic Substances Control recommends 0.1% in their Preliminary Endangerment Assessment Guidance Manual (USEPA, 1995b; Cal/EPA, 1994).

C. Recommendation

OEHHA recommends adopting 0.1% as the default value for dermal absorption of cadmium from soil, based on the Wester *et al.* (1992a) study.

F.1.3.4 Chromium (VI)

Recommended point estimate for dermal uptake: 1.0% (based on Clement Associates, 1988)

F.1.3.4.1 Studies Considered

Baranowska-Dutkiewicz (1981) found chromium (VI) from aqueous solutions to be readily absorbed by human skin. Seven volunteers were exposed to sodium chromate solutions (0.01, 0.1, and 0.2 M) on an area of the forearm for 15, 30 or 60 minutes, in a series of experiments. The exposure area was covered with a watch glass throughout the exposure period. Absorption was calculated from the difference between the applied and recovered dose of chromium (VI). The authors reported that percutaneous absorption of chromium is dependent on both concentration and time. Specifically, they found that (1) absorption was highest from the 0.01 molar solution (7.7-23% of applied dose) and lowest from the 0.2 molar solution (3.4-10.6% of applied dose), (2) the rate of absorption decreased as exposure time increased, and (3) the rate of absorption increased as exposure concentration increased. Individual data were not provided.

Wahlberg and Skog (1965) used disappearance measurements of radiolabeled chromium to estimate and compare dermal absorption rates of trivalent and hexavalent chromium compounds *in vivo* in guinea pigs. Animals were exposed for 5 hours to various concentrations (0.00048 - 1.689 molar) of chromic chloride (Cr^{3+} carrier) or sodium chromate (Cr^{6+} carrier) labeled with ^{51}Cr. Dermal absorption of chromium was confirmed qualitatively by organ analysis. The maximal disappearance of hexavalent chromium was observed from a 0.261 molar solution: of the 10 animals exposed to this concentration, the mean disappearance percentage per 5-hour period was 4% of the applied dose (5-6% disappearance/5-hr period was measured for 3 of the 10 animals in this group). Dermal absorption was greater for hexavalent chromium than for trivalent chromium.

Czernielewski *et al*. (1965) also exposed guinea pigs to chromium (VI) as sodium chromate solution labeled with Cr^{51}. A single dose (15 µg chromium in 0.1 ml solution) was applied to a shaved area of skin for 24 hours (n=9 animals). Absorption was estimated by measurement of the Cr^{51} content of the following: urine, feces, blood (1 ml), heart, liver, spleen, adrenals, kidneys, lungs, lymphatics, and skin. Dermal absorption of chromium (VI) was estimated to be 1.3% of the applied dose from the 24 hour exposure. An additional group of 3 animals, whose skin had been pretreated with sodium hydroxide (3 drops of 0.5 n NaOH, 3 minutes per day for 1 week), were also exposed for 24 hours to the labeled sodium chromate solution. In these animals, 12.5% of the applied dose was absorbed per 24 hours.

Wahlberg (1965) determined disappearance rates for sodium chromate solutions applied to both human and guinea pig skin *in vitro*. Solutions (0.034 molar, pH 8.7) were labeled with ^{51}Cr and applied to skin samples for up to 48 hours. Disappearance rates were measured from the observed decrease in radioactivity of the donor solution over time. The rate of disappearance of chromium (VI) during a 5-hour period was 38 mμM $cm^{-2}hr^{-1}$ through guinea pig skin compared to 11 mμM $cm^{-2}hr^{-1}$ through human skin. These values were compared to a disappearance rate of 42 mμM $cm^{-2}hr^{-1}$ for guinea pig skin *in vivo*.

F.1.3.4.2 Selection of Absorption Value

A. Discussion

While chromium (VI) has been shown to be absorbed dermally by humans and guinea pigs, the quantitative data available on dermal absorption of chromium (VI) are limited.

Baranowska-Dutkiewicz (1981) provide the only quantitative data in humans. In this study, absorption was quantified using disappearance techniques. The reliability of these methods for quantifying absorption has been questioned, as total recovery of the chemical is not assured (USEPA, 1992; Wester and Maibach, 1983). This has been shown to result in an overestimation of absorption for some volatile compounds; although it has not been demonstrated with metals. The exposure sites in Baranowska-Dutkiewicz (1981) were occluded. Occlusion can alter skin hydration and temperature, and may result in greater absorption than what might occur under conditions where skin is not occluded (USEPA, 1992). In addition, it is difficult to predict how well data on dermal absorption of chromium (VI) from aqueous solutions compares with absorption of chromium (VI) from soil. Wester *et al.* (1992a, 1993b) compared dermal absorption of cadmium and arsenic from both water and soil. In these studies, the binding behavior of the metals in water to powdered stratum corneum and to soil was determined. For cadmium, the binding from water to soil was greater than the binding from water to powdered stratum corneum. At the same time, dermal absorption of cadmium in soil was much lower than in water (0.1% versus 9-13%, respectively). In the arsenic study, the binding capacity to soil and to powdered stratum corneum was relatively similar, as was the absorption of arsenic from water and from soil (2-6% and 3-5%, respectively). Further experiments on chromium (VI) are necessary in order to determine how absorption from water may differ from soil. Finally, the Baranowska-Dutkiewicz (1981) study consisted of a small number of subjects (n=7) and required multiple exposures. Together, these factors make it difficult to estimate a default point estimate for the dermal absorption of chromium (VI) from soil based on these data. However, these data do suggest that 1%, the default value currently in use (see Section 11.B. below) may be too low.

Data provided by Wahlberg and Skog (1965) and Czernielewski *et al*. (1965) also suggest that 1% may not adequately describe dermal absorption of chromium (VI). Under the conditions of these studies, absorption ranged from 1-12% in guinea pigs. It is

unclear, however, how well absorption data from guinea pigs approximates absorption in humans. USEPA (1992) suggests that, in general, dermal absorption is greater in guinea pigs than humans. This is consistent with data from Wahlberg (1965) which showed that the rate of absorption through guinea pig skin was greater than through human skin *in vitro*. The extent that dermal absorption differs between humans and guinea pigs is still unknown.

B. Other Agencies' Default Values

The most recent CAPCOA guidelines recommend using 1% as the dermal absorption point estimate for chromium (VI) (CAPCOA, 1993). This number is based on Clement Associates (1988) which suggests using a default of 1% for inorganic chemicals when quantitative data are not available to estimate chemical-specific dermal absorption fractions from soil. USEPA Region IX also suggests 1% as the default point estimate for chromium (VI) (USEPA, 1995b).

C. Recommendation

Until further data are available (data on chromium (VI) allowing determination of a chemical-specific number, or data on other inorganics suggesting a more appropriate default value for this class of chemicals), OEHHA recommends adopting 1% as the default point estimate for dermal uptake of chromium (VI).

F.1.3.5 Inorganic Lead

Recommended point estimate for dermal uptake: 1.0% (Clement Associates, 1988)

F.1.3.5.1 Studies Considered

Bress and Bidanset (1991) studied percutaneous absorption of lead *in vitro* using human abdominal skin obtained from autopsy, and guinea pig dorsal skin. Lead oxide or lead acetate (10 mg) were applied to 1.3 cm^2 skin samples. After 24 hours, the lead content of the saline reservoir fluid was measured. The lead content of the skin samples after exposure was not measured. In this experiment, 0.05% of the applied dose of lead acetate was recovered in the reservoir fluid, and less than 0.01% of the lead oxide. There was no difference between human and guinea pig skin. Bress and Bidanset (1991) also examined *in vivo* percutaneous lead absorption in guinea pigs. Lead acetate or lead oxide, mixed in aqueous solution, were applied to a shaved area (2 cm^2) of the back (300 mg lead per kg body weight). After exposure for 1 week, the animals were killed and lead was measured in blood, brain, liver and kidney. Percent of applied dose absorbed could not be determined from this study. However, the concentration of lead in the measured tissues following lead oxide exposure was consistent with that from control animals. In contrast, the lead concentration in measured tissues following lead acetate exposure was greater than controls, although absorption was considered poor, and statistics were not provided.

Moore *et al.* (1980) studied percutaneous absorption of lead acetate in humans from two commercial hair dye products. The products (one a lotion and one a cream) were spiked with lead-203 and applied to each subject's forehead (n=8) for 12 hours. The preparations were applied in various forms (wet and dried) with periods of one month between each application. Lead absorption was estimated from blood counts, whole-body counts, and urine activity. Results were normalized for each subject by administration of an intravenous tracer dose of lead-203 chloride. The mean uptake of lead-203 activity, measured in whole body at 12 hours, was greatest when the preparation was dried and skin was slightly abraded (0.18 ± 0.339% of applied dose). The mean absorption including all methods of application (measured in whole body at 12 hours) was 0.058 ± 0.081% with a range of 0-0.3%.

Lilly *et al.* (1988) conducted a series of studies in humans using sweat, saliva, blood and urine to monitor lead absorption through skin. Lead nitrate (0.5 M solution; applied dose of 6.2 mg lead) was dispensed onto filter paper and placed on the left arm of a single volunteer. The paper was covered with 'Parafilm', held in place with plastic wrap, and left for 24 hours. Sweat samples were taken from the unexposed arm and analyzed for lead content. The authors reported a rapid increase in the concentration of lead in sweat taken from the unexposed arm, from an initial concentration of 25 μg Pb/liter to 261 μg Pb/liter (at 21 hours of exposure) and 370 μg Pb/liter (one day after exposure). In similar experiments (n=unknown), lead was measured in blood, urine and saliva in addition to sweat. The authors reported that, along with an increase in lead in sweat sampled from the unexposed arm, lead concentrations significantly increased in saliva. In one subject, lead concentration in saliva increased from an initial average of 15 μg Pb/liter to 115 μg Pb/liter after 3 hours of exposure. In contrast, lead concentrations in urine and blood did not increase significantly. Lilly *et al.* (1988) also examined lead absorption using lead metal and lead oxide powder in place of lead nitrate. They reported that the concentration of lead absorbed into the skin appears to be dependent on the extent to which a person sweats (i.e., when the exposed arm was moist from the subject's sweat, a greater amount of lead was measured in sweat samples taken from the unexposed arm, compared to when the exposure area remained dry.)

More recently, Stauber *et al.* (1994) reported on additional *in vivo* work regarding percutaneous absorption of inorganic lead compounds in humans. It appears this work comes from the same laboratory as the Lilly *et al.* (1988) study. Using similar research protocols as described above, these authors examined dermal lead absorption using lead nitrate, and lead nitrate spiked with lead-204. Again, they reported rapid increases in sweat samples from the unexposed arm, concomitant increases in lead concentrations in saliva, but only small concentrations of lead in blood and urine. In order to quantify dermal lead absorption, 4.4 mg lead (as 0.5 M Pb $(NO_3)_2$) was dispensed onto filter paper and secured with plastic wrap to the left arm of one subject. After 24 hours, the filter paper was removed and the arm was washed. Of the 4.4 mg lead, 3.1 mg was recovered from the filter paper and wash fluid. Using this disappearance technique, the authors estimated that 29% of the lead was absorbed.

F.1.3.5.2 Selection of Absorption Value

A. Discussion

Quantitative data on percutaneous absorption of lead in humans are limited. Human exposure data from Moore *et al.* (1980) suggest that absorption of lead is quite poor via the dermal exposure pathway. However, in this study lead was applied in cream and lotion which are not considered relevant vehicles for our purposes.

The work reported by Lilly *et al.* (1988) and Stauber *et al.* (1994) do not provide enough information to quantify the amount of lead absorbed via skin, and with few subjects and occluded exposure scenarios it is difficult to extrapolate from these data to the general population. These studies do, however, demonstrate that dermal lead absorption in humans does occur and can be measured in sweat and saliva. In addition, these data indicate that lead absorption via skin is just barely detectable in blood, which may help explain low absorption estimates reported by Moore *et al*. (1980). It has also been suggested that the presence of colloidal sulphur in the lead acetate formulations used by Moore *et al.* (1980) may have led to the formation of insoluble lead sulphide, which would not be likely to be absorbed through skin (Stauber *et al.*, 1994).

B. Other Agencies' Default Values

The most recent CAPCOA guidelines recommend 0.1% as the dermal absorption point estimate for lead (CAPCOA, 1993). Cal/EPA's Department of Toxic Substances Control (DTSC) currently recommends using 1% as the default dermal absorption value for lead, based on Clement Associates (1988). [Note: Clement Associates (1988) suggests using a default value of 1% for inorganic chemicals when quantitative data are not available to estimate chemical-specific dermal absorption fractions from soil.] USEPA does not currently recommend a number for dermal absorption of lead.

C. Recommendation

Until further data are available (data on lead allowing determination of a chemical-specific number, or data on other inorganics suggesting a more appropriate default value for this class of chemicals), OEHHA recommends adopting 1% as the default point estimate for dermal uptake of lead. This value is consistent with Cal/EPA's DTSC.

F.1.3.6 Mercury

Recommended point estimate for dermal uptake from soil: 10%

F.1.3.6.1 Studies Considered

A. Key Study

Baranowska-Dutkiewicz (1982) exposed the forearms of eight male volunteers to aqueous mercuric chloride solutions. Aliquots (0.25 ml) of $HgCl_2$ solutions were applied directly to a 22 cm^2 area of skin and covered with a watch-glass. Percutaneous

absorption of mercury was calculated as the difference between the amount applied and the amount recovered after the skin and the watch-glass were washed. In order to examine the effect of concentration on uptake, 3 concentrations (0.01, 0.1, and 0.2 M) were applied for 30 minutes. It was reported that, as concentration increased, rate of uptake increased. In order to examine the influence of exposure time on uptake, 0.1 M $HgCl_2$ was applied for 5, 10, 15, 30 and 60 minutes. The authors reported that the average rate of uptake of mercury decreased from 9.3 μg/cm^2/min during a 5 minute exposure, to 2.5 μg/cm^2/min during a 1 hour exposure. The average percutaneous absorption of mercury was calculated for the various time points (5, 10, 15, 30, and 60 minutes) to be 20%, 29%, 37%, 60% and 64% of applied dose, respectively.

The only data available regarding percutaneous absorption of mercury from soil comes out of the Wester laboratory. Data from *in vitro* experiments examining absorption of mercury ($^{203}HgCl_2$) in soil through human skin were presented at the Society of Toxicology Annual meeting and are published in abstract form (Wester et al., 1995). $^{203}HgCl_2$ in soil was administered to human skin (0.5 μg/cm^2 containing 1 μCi) for 24 hours. Using soil loads of 5, 10, and 40 mg, skin content of mercury was 10.4 ± 6.8%, 6.1 ± 2.0%, and 7.2 ± 10.8% of dose, respectively. The authors concluded that human skin has great capacity to accumulate mercury (as mercuric chloride) from soil and that it probably does become absorbed systemically.

B. Other Studies

Wünscher *et al.* (1991) examined percutaneous absorption of mercury vapor in rats after subchronic exposure. The purpose of this study was to determine the suitability of the rat tail as a model of mercury skin absorption. The authors were able to confirm that mercury was absorbed through rat tail skin, and then accumulated in the kidney. However, the rate of uptake was not quantified.

Hursh *et al.* (1989) studied dermal absorption of mercury vapor in humans. Each of 5 men exposed the skin of one forearm (a single exposure) to vapors with concentrations ranging from 0.88-2.14 ng $^{203}Hg/cm^3$ for periods of 27 to 43 minutes. The rate of dermal uptake of mercury by the arm was quantified by measuring the difference between accumulated radioactivity on exposed and unexposed forearms following exposure. The mean uptake rate for the 5 subjects was reported as 0.024 ng Hg per cm^2 skin per minute per ng Hg per cm^3 air. At this rate, the authors estimate that dermal absorption of mercury from vapor is approximately 2.6% of the rate of uptake by the lung. In addition, the study protocol included a procedure in which adhesive strips were applied every 3-4 days post exposure which regularly removed cells of the stratum corneum from the same marked skin area following exposure. The authors reported that, while they believe that the stratum corneum did not form a barrier to the absorption of mercury vapor, approximately half of the mercury taken up by the skin is lost in the normal shedding of epidermal cells as mercury-containing cells below the stratum corneum migrate outward.

F.1.3.6.2 Selection of Absorption Value

A. Discussion

The data available on percutaneous absorption of mercury are quite limited.

Baranowska-Dutkiewicz (1982) provided quantitative data on dermal absorption of mercury in humans using a disappearance technique to estimate absorption. The reliability of disappearance techniques for quantifying absorption has been questioned, as total recovery of the chemical is not assured (USEPA, 1992; Wester and Maibach, 1983). This has been shown to result in an overestimation of absorption for some volatile compounds; however, it has not been demonstrated with metals. In any case, results from this study show that over 60% of applied dose was possibly absorbed after exposure to mercuric chloride for 1 hour. Because the area of exposure was occluded, and because of the overestimation inherent in the disappearance technique employed, this value may represent a high end estimate of dermal absorption. Occlusion can alter skin hydration and temperature and may result in greater absorption than what might occur under conditions where skin is not occluded (USEPA, 1992). However, with such relatively short exposure periods in this study (5 minutes to 60 minutes), this may not have had any affect on absorption. (Note: even after only 5 minutes of exposure, 20% of applied dose was absorbed.)

Even if the results of Baranowska-Dutkiewicz (1982) are high, or provide more of a high end estimate of percutaneous absorption from water, preliminary data from Wester's group suggest that the current default value of 1% from soil (see Section II.B. below) is too low. This is the only available study regarding dermal absorption of mercury from soil. Using *in vitro* techniques, skin contained as much as 10% of applied dose after 24-hour exposure. This does not include any mercury recovered in the receptor fluid. In addition, *in vitro* techniques may underestimate absorption, as they may not accurately mimic metabolic processes of living systems (USEPA, 1992).

It is difficult to predict how well data on dermal absorption of mercury from an aqueous solution (as in Baranowska-Dutkiewicz, 1982) compares with absorption of mercury from soil. Wester *et al.* (1992a, 1993b) compared dermal absorption of cadmium and arsenic from both water and soil. In these studies, the binding behavior of the metals in water to powdered stratum corneum and to soil was determined. For cadmium, the binding from water to soil was greater than the binding from water to powdered stratum corneum. At the same time, dermal absorption of cadmium in soil was much lower than in water (0.1% versus 9-13%, respectively). In the arsenic study, the binding capacity to soil and to powdered stratum corneum was relatively similar, as was the absorption of arsenic from water and from soil (2-6% and 3-5%, respectively). From the preliminary *in vitro* data of the Wester *et al.* (1995) abstract, it appears that absorption of mercury from water may be greater than from soil; however, further experiments on mercury are necessary in order to determine how absorption from water may differ from soil.

B. Other Agencies' Default Values

California's Department of Toxic Substances Control (DTSC) suggests using 1.0% as the default point estimate for dermal absorption of mercury from soil in their Preliminary Endangerment Assessment Guidance Manual (Cal/EPA, 1994). The CAPCOA (1993) guidelines also recommend using a default of 1.0% for mercury. In both cases, the 1.0% value is based on the Clement Associates' Multi-Pathway Health Risk Assessment Input Parameters Guidance Document (Clement Associates, 1988) which suggests use of 1.0% for inorganics, based on an order-of-magnitude approach, as a default value in the absence of data sufficient to calculate a chemical-specific value.

C. Recommendation

Although the data on dermal absorption of mercury are limited, data from Baranowska-Dutkiewicz (1982) and Wester *et al.* (1995) indicate that the current default of 1% is too low. Data from Baranowska-Dutkiewicz (1982) indicate that absorption may be as high as 64% under conditions of occlusion. At this time, based on an order-of-magnitude approach, OEHHA recommends adopting 10% as the default dermal absorption value for mercury.

F.1.3.7 Nickel

Recommended point estimate for dermal uptake from soil: 4%

F.1.3.7.1 Studies Considered

A. Key Study

Fullerton et al. (1986) examined the permeation of nickel salts, specifically nickel sulfate hexahydrate and nickel chloride hexahydrate, through human skin in vitro. Skin excised in surgery was exposed to 184 $\mu g/cm^2$ nickel salt solution. In the first experiment the effect of occlusion on the permeation rate of nickel chloride was examined. Occlusion resulted in a significantly higher permeation rate (approximately 3.6 percent of applied dose) compared with non-occluded exposure (approximately 0.23 percent) after 144 hours.

In the second experiment, Fullerton et al (1986) the effect of the type of nickel salt was examined under occlusive conditions. Nickel ions from a chloride solution passed through the skin about 50 times faster than nickel ions from a sulfate solution. The amount of permeation of nickel chloride was much higher (16%) at 144 hours than nickel sulfate (0.3%). The authors concluded that nickel was capable of penetrating the skin barrier, but the process was slow, having a lag-time of about 50 hours. The occluded-skin permeation of nickel chloride was considerably higher in experiment 2 than experiment 1 (9-16% vs 3.6%) and was attributed by the authors to the use of skin from different donors.

B. Other Studies

Spruit et al. (1965) utilizing human cadaver skin have shown that nickel is absorbed by the dermis. Nickel penetrates deeper at sweat ducts and hair follicles and has a special affinity for keratin.

Dermal appication of 60 mg Ni/kg or higher (nickel sulfate) resulted in microscopic changes in the liver and testis of rats indicating that absorption can occur from the intact skin (Mathur et al., 1977). However, it should be noted that under these experimental situations skin injury did occur and therefore may have allowed easier passage of nickel through the injured tissue. It was not possible to estimate the percent absorption from the data.

F.1.3.7.2 Selection of Absorption Value

A. Discussion

It is difficult to predict how well absorption of nickel from a chloride or sulfate solution compares to absorption from nickel in soil on the skin. Wester *et al.* (1992a, 1993b) compared dermal absorption of cadmium and arsenic from both water and soil. In these studies, the binding behavior of the metals in water to powdered stratum corneum and to soil was determined. For cadmium, the binding from water to soil was greater than the binding from water to powdered stratum corneum. At the same time, dermal absorption of cadmium in soil was much lower than in water (0.1% versus 9-13%, respectively). In the arsenic study, the binding capacity to soil and to powdered stratum corneum was relatively similar, as was the absorption of arsenic from water and from soil (2-6% and 3-5%, respectively). We have chosen the value of 4% based on the absorption of nickel from a chloride solution in Fullerton et al. (1986).

B. Other Agencies' Default Values

California's Department of Toxic Substances Control (DTSC) suggests using 1.0% as the default point estimate for dermal absorption of nickel from soil in their Preliminary Endangerment Assessment Guidance Manual (Cal/EPA, 1994). The CAPCOA (1993) guidelines also recommend using a default of 1.0% for mercury. In both cases, the 1.0% value is based on the Clement Associates' Multi-Pathway Health Risk Assessment Input Parameters Guidance Document (Clement Associates, 1988) which suggests use of 1.0% for inorganics, based on an order-of-magnitude approach, as a default value in the absence of data sufficient to calculate a chemical-specific value.

C. Recommendation

Although the data on dermal absorption of nickel are limited, data from Fullerton et al (1986) indicate that the default value of 1% may be too low under certain circumstances (e.g., occlusion and for certain salts. We are recommending 4% based on

the results of Fullerton et al (1986). Although in most exposure scenarios, occlusion does not occur, we note the difference in absorption of the two nickel salts. This indicates that the old default value of 1% may be too low and inadequately protective.

F.1.4 Dermal Absorption of Organic Compounds

F.1.4.1 Dermal Absorption Fraction for Polychlorinated Biphenyls (PCBs)

Recommended point estimate for dermal uptake from soil - 14 percent

F.1.4.1.1 Studies Considered

A. Key Study. (Wester, et al., 1993a)

The dermal uptake of each of two commercial PCB formulations was studied in Rhesus monkeys. The formulations were Aroclor 1242 (42 percent chlorine - 3% mono-, 13% di-, 38% tri-, 30% tetra-, 22% penta-, and 4% hexachlorobiphenyl (HSDB, 1996)) and Aroclor 1254 (54 percent chlorine - 11% tetra-, 49% penta-, 34% hexa-, and 6% heptachlorobiphenyl (HSDB, 1996)). Each PCB preparation was adsorbed onto soil particles that before sieving contained 26 percent sand, 26 percent clay, 48 percent silt, and 0.9 percent organic carbon. The soil was fractionated by particle size to obtain a sample that passed through 48-mesh and was retained by 80-mesh (180 - 300 μM according to Wester, et al., (1993a)). The soil levels of the PCB preparations were 44 ppm Aroclor 1242 and 23 ppm Aroclor 1254.

Adult female rhesus monkeys were dermally exposed to the soil laden PCBs. The samples were applied for 24 hours to a 12 cm^2 area of lightly shaved abdominal skin which was protected by a non-occluded patch. The applied doses were 1.75 $\mu g/cm^2$ Aroclor 1242 and 0.91 $\mu g/cm^2$ Aroclor 1254. The soil loadings were 40 mg soil / cm^2 skin for both preparations. Following the first 24 hour exposure during which systemic absorption was measured as the content recovered in urine and feces, the patch was removed, the visible soil was removed from the site of application, the treated skin was washed with soap/water, and urine/feces were collected for an additional 34 days. The total exposure duration was 24 hours and the total collection time was 35 days.

The cumulative urine/feces recovery over the 35 day exposure interval was 7.69 ± 2.38 percent Aroclor 1242 and 3.77 ± 0.28 percent Aroclor 1254. The recovery of Aroclor 1242 and 1254 following intravenous (iv) administration was determined from a previous study (reference not cited) as 55.5 ± 5.1 percent and 2F.1 ± 7.5 percent, respectively. The fractional absorption was calculated as: 7.69/0.555 = 0.139 for Aroclor 1242 and 3.77/0.267 = 0.141 for Aroclor 1254.

B. Other Studies

The dermal absorption of purified 3,3',4,4'-tetrachlorobiphenyl (TCB) from soil was studied in rat (*in vivo* and *in vitro*) and in human (in vitro) (USEPA, 1992). The protocol and analysis followed that described for dioxin in Section F.1.7. Briefly, rats were dermally exposed *in vivo* to soil bound TCB (1,000 ppm) at an applied dose of 10 $\mu g/cm^2$ and a soil loading of 10 mg/cm^2 skin. The organic content of the soil was 0.45 percent and this soil formulation is referred to as LOS. After 96 hours, 49.7 ± 10.0 percent of the applied dose was found in the urine, feces, and tissues. No measurements were taken at earlier intervals. The *in vitro* studies were carried out for 96 hours and measurements were also taken at earlier intervals, including 24 hours. The *in vitro* rat study also used a high organic content (HOS, 11.2 percent) soil at a soil loading of 10 mg/cm^2. Human, *in vivo* equivalent ABSs from LOS and HOS were calculated from the human *in vitro*, rat *in vivo* and rat *in vitro* data, using direct proportions for *in vivo* vs. *in vitro* absorption and the 24 hour vs. 96 hour fractional retention in washed skin. The final results were expressed as a human ABS for TCB of 2.1 percent for LOS and 0.63 percent for HOS. USEPA (1992), considered the range too narrow in light of the uncertainties inherent in the methodology and therefore reported a final recommendation of a soil ABS range for TCB of 0.6 to 6 percent.

Hughes, et al. (1992) studied the effects of physical form on the *in vivo* dermal uptake of purified 2,2',4,4',5,5'-hexachlorobiphenyl (HCB) (255-268 $\mu g/cm^2$) and 3,3',4,4'-tetrachlorobiphenyl (TCB) (48-49.6 $\mu g/cm^2$) on 90 day old female Fischer 344 rats. In this study, no soil was used, but the intent was to determine how the application of HCB or TCB in volatile solvent (ethanol), as a solid, or as a water paste or suspension affected the absorption. Systemic absorption was followed in urine, feces and tissues for 24 hours, at which time the exposed skin was washed and the collection of samples continued for a total of 5 days. Because the exposed skin was protected by an occlusive patch, the role of humidity and increased skin temperature could not be separated from affect of the physical forms. Under the occlusive conditions, for HCB, a total of 5.3 ± 0.3 percent (from ethanol) and 8.0 ± 0.2 percent (solid) was absorbed. For TCB the total absorption was 6.1 ±1.3 percent (ethanol) and 7.8 ± 1.0 percent (solid). Absorption from the aqueous paste or suspension was intermediate. After the first 24 hours, about 80 percent of the applied HCB dose was washable from the skin while about 60 percent of the applied TCB was washed from the skin. Treated skin, however, did retain some of the applied chemicals, i.e. the amount not washed off at 24 hours. For HCB, about 10 percent of the applied dose was found at the skin application site at 5 days post-exposure, and for TCB, about 30 percent was found.

Fisher, et al. (1989) compared the *in vivo* dermal uptake of purified 2,2',4,4',5,5'-hexachlorobiphenyl (HCB) from acetone, between young (33 day old) and mature (82 day old) female Fischer 344 rats. The applied dose was 103 $\mu g/cm^2$ for each group and the exposure duration was 5 days. The absorbed HCB was measured in urine, feces, tissues and carcass. After the 5 day interval the total absorption was 44.7 ± 3.1 percent for the young rats and 42.4 ± 2.8 percent for the mature rats. When the data were further

analyzed by ANOVA, the absorption by the young rats was greater than that by the mature rats, in particular at early times (e.g. 6 hours).

F.1.4.1.2 Selection of Absorption Value

A. Discussion

The Wester, et al. (1993a) study is the only *in vivo* study on the uptake of a complex mixture of PCBs from soil. Under most normal human environmental exposures, PCBs will be present as a mixture and data from such preparations will be more relevant for human exposures. In the two formulations in the Wester, et al. (1993a) study, one was dominated by the lower chlorinated congeners (Aroclor 1242) and the other was dominated by the higher chlorinated congeners (Aroclor 1254). Despite this difference in congener representation, the calculated ABS values were similar, i.e. ABS is 14 percent for each preparation. These results suggest that under the conditions of the experiment, the dermal uptake from soil may be similar for all PCB congeners. Comparative soil uptake data on individual congeners are not available. The study described by USEPA (1992) used only TCB and the HCB/TCB study described by Hughes, et al. (1992) did not use soil. In the latter study, which included HCB or TCB as a solid, the total absorption after 5 days was similar (5 - 6 percent). However, differences were observed for the amount of PCB washed off the skin and that which was retained by the exposed skin. Similar experiments that incorporate soil would be helpful to better understand the processes involved in the dermal uptake of the PCBs from soil.

The analysis by USEPA (1992) requires an assumption of similar kinetics for the soil uptake of TCB between species (human and rat) and between study type (*in vitro* and *in vivo*). The absence of *in vivo* data for times less than 96 hours prevents verification of this assumption. Another assumption in the USEPA (1992) analysis is the equivalence of the fraction of the non-washable TCB dose in the skin between 24 and 96 hours, and this assumption has not been verified. The issue of exposure time was discussed in the USEPA (1992) document in another chapter (p.4-2), wherein caution is expressed about assuming that percent absorption will be the same at all time points. Hence the use of the TCB *in vitro* data to calculate *in vivo* uptake, needs verification. While the analysis provided by USEPA (1992) is an attempt to deal with the complexities of dermal absorption from soil, an ABS based on this analysis is not considered more or less reliable than that empirically derived from the Wester, et al. (1993a) study.

B. Other Agency Recommended Default Values

A soil ABS of 0.6 - 6 percent is recommended by USEPA (1992). An ABS of 6 percent is recommended by USEPA (1995b). A soil ABS of 15 percent is recommended by CalEPA (1994) and CAPCOA (1993).

C. OEHHA Recommendations

A soil point estimate soil ABS for PCBs is recommended as 14 percent, based on the data of Wester, et al. (1993a). The value is based on the ABSs of two PCB

formulations in which one was dominated by the tri- and tetra congeners (68 percent, Aroclor 1242) and the other was dominated by the penta- and hexa congeners (83 percent, Aroclor 1254).

F.1.4.2 Dermal Absorption Fraction for Polychlorinated dibenzo-p-dioxins and dibenzofurans (as TCDD)

("Dioxin" emissions are reported as TCDD equivalents. Therefore, for purposes of the Hot Spots program, all polychlorinated dibenzo-p-dioxins and dibenzofurans are considered to have the same dermal absorption characteristics as "TCDD").

Recommended point estimate for dermal uptake from soil - 2 percent**.**

F.1.4.2.1 Studies Considered

A. Key Study

In Shu, et al. (1988), soil-bound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was applied to the backs of rats, clipped of hair. Laboratory contaminated TCDD soil was prepared from soil obtained from Times Beach MO and determined not to contain TCDD before the experimental addition of the chemical. Environmentally contaminated soil was also obtained from Times Beach MO and determined to contain 123 ppb TCDD. Soil loading was 20.8 mg soil/cm^2 skin on a total skin area of 12 cm^2. The TCDD content of the laboratory prepared soil was 10 or 100 pg/mg soil. Occlusion of the skin was minimized by the use of a perforated aluminum eye patch to cover the exposed area. Dermal exposure duration to the TCDD-laden soil was 24 hours and recovery was measured 48 hours following initiation of exposure. In some experiments, 0.5 or 2.0 percent (w/w) used crankcase oil was added to the soil before the addition of TCDD, except for the 100 pg/mg soil (20.8 ng / cm^2 skin) sample, and soil that was environmentally contaminated with TCDD.

Following 24 hour dermal exposure + 24 hour post-exposure (total of 48 hours from initiation of exposure), the TCDD contents of the liver were determined. The percent uptake of TCDD in liver was not affected by the applied TCDD dose (12.5, 125 ng/kg body weight), the presence of crankcase oil in the soil, the use of soil that had been environmentally contaminated with TCDD, or the use of haired or hairless rats. The uptake of TCDD under the experimental protocols ranged from 0.54 ± 0.06 to 1.01 ± 0.22 percent and averaged 0.76 ± 0.16 percent. The average liver TCDD content was corrected for incomplete recovery (15 percent) and incomplete absorption (30 percent), following oral administration of TCDD in corn oil. The absorption factor was calculated as (0.76 percent ÷ [0.15/0.30] = 1.5 percent. The calculation is based on the assumption that the source of fecal TCDD following oral exposure is unabsorbed TCDD. Diliberto, et al. (1996) point out that during the first 48 hours following oral exposure, TCDD in rat feces is derived from unabsorbed and absorbed TCDD. A change in the assumption of the contribution of absorbed TCDD to level of TCDD in the feces from 0 to 100 percent

would lead to an absorption fraction of 5 percent. However the data of Diliberto, et al. (1996) suggest at 48 hours, absorbed TCDD contributes only about 10 percent of the fecal TCDD.

B. Other Studies

Poiger and Schlatter (1980) measured the absorption of TCDD from a soil/water paste formulation (26, 350, or 1300 ng in 14.3 mg soil/cm^2 skin) in rat, and calculated a dermal uptake of 8.3 percent corrected for the uptake by liver following oral absorption from soil (Seveso). Measurements were taken 48 hours after the initiation of a 24 hour exposure period. A correction based on oral absorption from ethanol (50% v/v) resulted in a value of 5.4 percent. The authors also compared the liver uptake of dermally applied TCDD from a soil/water paste to the uptake from methanol, and found the soil/water paste caused a reduction in the fractional uptake (compared to methanol) of 12 percent (1.6 ng TCDD/kg BW) or 15 percent (5.8 ng/kg BW).

USEPA (1992) analyzed data on dermal absorption of TCDD from organic (HOS) and low organic (LOS) soils by rat (*in vivo* and *in vitro*) and by human (*in vitro*) during exposure intervals up to 96 hours. To derive an ABS for human *in vivo* uptake of TCDD from HOS, USEPA (1992) applied corrections by direct ratios to account for rat *in vivo*, rat *in vitro*, and human *in vitro* data, and to correct 96 hour absorption data for a 24 hour exposure interval. USEPA (1992) further estimated absorption from LOS from the estimated absorption derived from HOS by a direct ratio procedure. The results were expressed as a range of values: 0.1 percent for HOS, to 3 percent for LOS.

F.1.4.2.2 Selection of Absorption Value

A. Discussion

In the Shu, et al. (1988) study, dermal absorption was defined as the amount of systemically available chemical. This definition does not include the amount of TCDD retained by the skin at the site of application. Chemicals retained at the site of application may be associated with the stratum corneum and easily removed with solvent (or detergent) or they may be retained in the epidermal and dermal layers. Following dermal exposure to TCDD in acetone (0.05 to 321 μg/kg body weight for 3 days), 82 ± 3 percent of the TCDD contents remaining at the skin site of application was removed by acetone (Brewster, et al., 1989). Banks and Birnbaum (1991) observed that rats dermally exposed to 0.32 μg/kg TCDD in acetone exhibited a decrease in the percentage of total TCDD (80 to 44 percent) at the application site between days 1 and 5 and an increase in TCDD in the tissues (17-38 percent) during the same interval. The proportion of acetone washed to retained TCDD at the site of application was not given. The data suggest that over an extended period of time, dermally applied TCDD may become available for distribution to the tissues. Similar studies on soil-bound TCDD have not been published.

A major difference between Poiger and Schlatter (1980) and Shu, et al. (1988) is the presence of water added to the soil to make a soil/water paste in the former study. Poiger and Schlatter (1980) also used an occlusive patch of aluminum foil which could lead to a buildup of water vapor at the site of application. The increased water vapor may also lead to increased skin hydration that will affect dermal absorption. Because in the Poiger and Schlatter (1980) study, unlike the Shu, et al. (1988) study, the presence of moisture at the site of application could not be controlled, the Poiger and Schlatter (1980) study was not used to calculate the dermal uptake of TCDD.

The analysis by USEPA (1992) requires an assumption of similar kinetics for the uptake of TCDD from soil between species (human and rat) and between study type (*in vitro* and *in vivo*). However, according to the data presented by USEPA (1992, Table 6-4) this assumption is questionable, because the data show that during the 24 to 96 hour exposure duration, the percent absorption of TCDD from soil increased 3-fold for rat/*in vivo*, 5-fold for rat/*in vitro*, and 8-fold for human/*in vitro*. Another assumption in the USEPA (1992) analysis is the equivalence of the fraction of the non-washable TCDD dose in the skin between 24 and 96 hours, an assumption that was not verified in the USEPA (1992) document. Banks and Birnbaum (1991) showed that the fraction of dermally applied TCDD (from acetone) at the site of application (washed plus unwashed) decreased over a 5 day interval and increased in the tissues. The issue of exposure time was discussed in the USEPA (1992) document in another chapter, wherein caution is expressed about assuming that percent absorption will be the same at all time points (USEPA, 1992, p. 4-2). Hence, the use of the TCDD *in vitro* data to calculate *in vivo* uptake needs verification. While the analysis provided by USEPA (1992) is an attempt to deal with the complexities of dermal absorption, an absorption factor based on this analysis is not considered more or less reliable than that empirically derived from the Shu, et al. (1988) study.

Howd and McKone (1991) used a fugacity model that considers diffusion in and through skin, to predict a 12 hour dermal absorption factor for TCDD. When a soil loading of 5 mg/cm^2 skin is used, the 12 hour dermal absorption factor is predicted to be 11 percent.

Dermal absorption across rat skin is considered to be greater than for human (Wester and Maibach, 1975 and 1983). The conclusion, however, is based on chemicals that did not include TCDD. Other factors besides species specificity may affect the absorption of soil-bound TCDD. These factors include the nature of the soil and the pharmacokinetics of TCDD, and they are discussed below.

Umbreit, et al. (1988) demonstrated differing oral bioavailabilities in guinea pig livers of soil-bound TCDD, depending on the origin of the soil. Compared to TCDD in soil from Times Beach MO, TCDD from a contaminated site in Newark NJ was only 5 percent as available. The difference in the soil-dependent bioavailability could be due to soil composition, particularly the presence of carbonaceous material or to the nature of the application of the TCDD to the soil. In the case of Times Beach MO soil, TCDD was

applied to the soil surface over a relatively short interval, whereas the TCDD in the Newark NJ soil accumulated over a long period of time due to leakage from a nearby factory (Umbreit et al., 1986). Although the presence of other TCDD-like compounds in the soils could influence the uptake of TCDD, the data of Shu, et al. (1988) show similar dermal uptake of TCDD from uncontaminated or co-contaminated soil from Times Beach MO.

Conditions may exist under which toxicokinetic differences among the various polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans could affect dermal uptake. For example, under acute exposures to 0.1 μmol/kg body weight, more dermally applied tetrachlorodibenzofuran (TCDF) was absorbed than was TCDD (Brewster, et al., 1989). Dermal uptake during chronic exposure has not been reported. Two issues that remain to be resolved are the retention of each congener at the site of application and the effect of mixtures of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans on uptake, retention and elimination.

Age may be a factor in the absorption of TCDD-like compounds. Banks, et al. (1990) demonstrated young rats (10 weeks) absorb a greater proportion of dermally applied TCDD or 2,3,4,7,8-pentachlorodibenzo-p-dioxin than rats at 36 - 120 weeks of age. Differences in dermal absorption as a function of development were suggested by Wester and Maibach (1983) who suggested the preterm infant does not have a fully developed dermal barrier function. The large skin surface area to body weight ratio in newborn infants compared to adults will result in a greater systemic dose for chemicals dermally applied at the same surface area. Although this difference can be taken into account in controlled studies, such control will not be present under real-life exposure conditions.

Absorption may be increased during repeated exposure to low doses, as opposed to single short-term exposures. In a study designed to measure the proliferative and toxic responses to three dioxin congeners, mice were exposed dermally, two times per week for twenty weeks, to low doses of each congener (Hebert et al., 1990). The congeners were TCDD, 2,3,4,7,8-pentachlorodibenzofuran, and 1,2,3,4,7,8-hexachlorodibenzofuran. The severity of the dermal toxicity associated with each congener increased with increasing exposure frequency and/or duration. Hence, continuous dermal exposure to low levels of TCDD and TCDD-like compounds may have consequences not predicted by acute and *in vitro* data. Although the chemicals were applied from solvent and not from soil, continuous exposure to low levels should be considered when evaluating the extent of uptake of TCDD from soil.

B. Other Agency Default Values

Factors for dermal absorption from soil have been reported by the following agencies: CAPCOA (1993), 2 percent; USEPA (1992), 0.1 to 3 percent (see discussion above); USEPA (1995b), and CalEPA (1994), 3 percent. The 3 percent value recommended by USEPA (1995b) and CalEPA (1994) is based on the analysis provided in USEPA (1992) and represents soil of low organic content.

C. OEHHA Recommendation

OEHHA recommends a systemic dermal absorption factor from soil for TCDD of 2 percent, based on Shu, et al. (1988). According to this analysis, the correction for incomplete absorption is based on fecal TCDD and requires that orally derived fecal TCDD represents 100 percent unabsorbed compound. The data of Diliberto et al. (1996), however, suggests no more that 10 percent of the fecal TCDD is derived from the absorbed dose. Even if all the fecal TCDD were derived from absorbed TCDD, the resulting ABS would increase by only 2.5-fold. While the analysis of USEPA (1992) provides an alternate approach to this derivation, the assumptions inherent in the approach require verification, in particular the extrapolation of data from 96 hours exposure to 24 hours exposure. The empirical study of Shu, et al. (1988) provides sufficient data with which to calculate a fractional ABS.

F.1.4.3 Dermal Absorption Fraction for Polycyclic Aromatic Hydrocarbons as Benzo[a]pyrene (BaP)

Recommended point estimate for dermal uptake from soil - 13 percent

F.1.4.3.1 Studies Considered

A. Key Study

In Wester, et al. (1990), the dermal uptake of soil-bound BaP was studied *in vivo* in Rhesus monkey. The systemic absorption of soil-bound BaP was based on urinary excretion following exposure of 12 cm^2 abdominal skin to 10 ppm BaP in soil at a soil loading of 40 mg/cm^2 skin. The dermal application site was protected with a nonocclusive cover. Prior to sieving, the soil composition was 26 percent sand, 26 percent clay, and 48 percent silt with 0.9 percent organic carbon content. The soil particles in the experiments were obtained by sieving the soil and using the particles that passed through 48-mesh and were retained by 80-mesh. Exposure duration to the chemical laden soil was 24 hours, during which time urine was collected. The cover was removed, visible soil was collected, and the skin application site was washed with soap and water. Urine was then collected for 6 additional days for a cumulative recovery period of 7 days. Incomplete excretion of BaP was corrected by the urinary excretion of BaP following intravenous (iv) administration of the PAH in acetone. The authors report a 24 hour dermal absorption factor of 13.2 ± 3.4 percent (n=4).

B. Other Studies

Yang, et al. (1989) studied the *in vivo* systemic absorption in rat of BaP in soil (particle size < 150 μm), fortified with petroleum crude oil (1 percent (w/w)) to which ^{3}H-BaP was added. The final BaP level in the soil was 1 ppm and the soil loading was 9 mg/cm^2. The soil consisted of 46 percent sand, 18 percent clay and 36 percent silt, with an organic content of 1.6 percent. After 24 hours, 1.1 percent of the radioactive label was found in the rat urine and feces; no label was found in the tissues. By 96 hours (4 days)

the cumulative total of radioactive label in the excreta + tissues was 9.2 percent, of which 5.8 percent was in the feces.

F.1.4.3.2 Selection of Absorption Value

A. Discussion

Dermal absorption of polycyclic aromatic hydrocarbons (PAHs), based on the urinary excretion of 1-hydroxypyrene (1-HP), has been documented among petrochemical industry workers, including those who dig soil (Boogaard and van Sittert, 1995). Although no attempt was made to quantify the extent of absorption through dermal and inhalation routes, the results of the study strongly suggest dermal uptake is substantial and is mitigated by the use of appropriate protective clothing. Elovaara, et al. (1995) compared the levels of urinary 1-HP among 6 creosote workers compared to that expected from the inhalation of the known air levels of PAHs containing ≥ 4 rings. The calculations predicted higher levels of urinary 1-HP than could be accounted for solely from the inhalation route of exposure.

When the Rhesus monkey data of Wester, et al. (1990) are compared with the rat data of Yang, et al. (1989), the 24 hour calculated dermal systemic absorption from Rhesus monkey is found to be greater than the 24 hour uptake (retention + excretion) but close to the total 4 day recovery reported for rat (Yang, et al., 1989). Such results are unexpected from the *in vivo* dermal uptake data reported by Wester and Maibach (1983), wherein dermal absorption in rat is greater than that in humans or Rhesus monkey, based on chemicals that did not include BaP. The difference in soil-bound BaP content (or level of skin applied BaP) is probably not responsible for this apparent discrepancy. Although the relationship between exposure concentration and uptake is not easily evaluated, the *in vitro* dose-dependent uptake of BaP from acetone, in hairless guinea pig, suggests a decreased level of dermally applied BaP should lead to an increased fractional absorption (Ng, et al., 1992).

There are three possible explanations for the apparent discrepancy between the Wester, et al. (1990) and Yang, et al. (1989) results. (1) The organic contents of the soils are different (0.9 percent and 1.6 percent, respectively). Hence, the BaP in the Wester, et al. (1990) study may have been less tightly bound than in the Yang, et al. (1989) study, provided the soil composition did not change when it was sieved. In the Yang, et al. (1989) study petroleum crude oil (1 percent (w/w)) was a co-contaminant, and its presence may have affected the adherence of BaP to the soil particles. (2) Species specific relative absorption data obtained with chemicals in solvent vehicles may not be applicable to soil-bound chemicals. (3) The species specificity of dermal uptake may also be chemical specific. The chemicals in the Wester and Maibach (1983) study did not include BaP, and a species specificity study on the *in vivo* dermal uptake of BaP was not found. The species-dependent dermal uptake of BaP, in acetone, in an *in vitro* system, was described by Kao et al (1985), and the order was mouse> human ≈ marmoset>rabbit and rat>>guinea pig.

Howd and McKone (1991) used a fugacity model that considers diffusion in and through skin, to predict a 12 hour dermal absorption factor for BaP. When a soil loading of 5 mg/cm^2 skin is used, the 12 hour dermal absorption factor for BaP is predicted to be 16 percent.

In the Wester, et al. (1990) study, only 6 percent of BaP administered by iv to Rhesus monkey appeared in the urine after 7 days. This observation is consistent with feces as a major route of excretion for BaP (Foth, et al., 1988; Yang, et al., 1989; Moody, et al., 1995). Fecal excretion, however, is not the primary route of excretion for all PAHs. Naphthalene and phenanthrene (two- and three-ring PAHs, respectively) are excreted primarily through urine, due in large part to metabolism (Turkall, et al., 1994; Kadry, et al., 1995).

Storm, et al., (1990) studied the 24 hour *in vitro* uptake of BaP, in acetone, by the skin of humans, rats, mice, and guinea pig. After the skin samples were washed with soap/water, 30 - 60 percent of the dermally applied BaP was found in the skin. In a similar *in vitro* experiment, Wester, et al (1990) observed 5 percent of BaP applied in acetone, remained bound to skin after 25 minutes, whereas 0.14 percent remained bound when soil was the vehicle. Chu, et al., (1996) studied skin retention of solvent applied BaP, *in vivo*, in hairless guinea pig, and observed 10 percent remained bound after 24 hours following soap/water washes. Additional data in the Chu, et al. (1996) study suggest migration from the skin into the systemic circulation, but the use of different applied doses prevents an unequivocal conclusion. A major difficulty with interpreting data obtained after washing skin with soap/water, is the presence of a "wash-in" phenomenon wherein soap aids in the retention of BaP (Moody, et al., 1995). Because PAHs may be metabolized in the skin to electrophilic metabolites that form DNA-adducts (Philips, et al., 1990), the retention of PAHs (or metabolites) by skin could serve as a reservoir for future biological effects. These phenomena, in particular the effect of detergent wash on the skin retention of soil-bound BaP, compared to solvent dissolved BaP, deserve further study.

The calculation of dermal uptake was based on studies in which BaP was administered as a single chemical (Wester, et al., 1990). PAHs, in the environment, however, usually occur as mixtures, e.g. bitumen, creosote, coal tar, diesel exhaust (see Philips, et al., 1990), and the properties of each PAH in the mixture may not always be the same as that of the pure compound. For example, the half-life of BaP, estimated from mouse skin, *in vivo*, was increased by 1.8 to 6.9-fold in the presence of other PAHs contained in various boiling fractions of coal-derived organic mixtures (Dankovic, et al., 1989). Hence, the studies described herein may not address scenarios that include exposure to mixtures.

B. Other Agency Default Values

USEPA (1992) does not recommend a dermal absorption factor for BaP from soil. The following absorption factors are recommended by other agencies: 10 percent (default

screening value) (USEPA, 1995), 3 percent (CAPCOA, 1993), and 15 percent (CalEPA, 1994, based on Wester, et al. (1990)).

C. Recommendation

OEHHA recommends a soil point estimate ABS for BaP of 13 percent. The recommendation is based on the *in vivo* Rhesus monkey study of Wester, et al. (1990).

F.1.4.5 Dermal Absorption Fraction for Hexachlorocyclohexanes

Recommended point estimate for dermal uptake from soil – 10%

F.1.4.5.1 Studies Considered

A. Key Study

The only study located regarding dermal absorption of hexachlorocyclohexane (HCH) from soil was that of Duff and Kissel (1995) who conducted *in vitro* dermal absorption studies using human cadaver skin and lindane-contaminated soils. Two types of soil were used: sandy loam (3.87% organic carbon content) and silt loam (0.73% organic carbon content). The studies were carried out for 24 hours with soil loading at 1, 5 or 10 mg/cm^2. Results of this study showed that most of the mass of absorbed lindane was found in the skin. Mean 24-hour dermal absorption values ranged from 0.45 to 2.35%, depending on soil load and soil type. The relative percent absorption increased significantly with decreases in soil load. In addition, approximately 40% of the lindane was lost to volatilization with a soil load of 1 mg/cm^2, while significantly lesser amounts were lost in the higher loading trials (less than 10% for the sandy loam soil at 10 mg/cm^2; less than 20% for the silt loam soil at 10 mg/cm^2).

B. Other Studies

Feldman and Maibach (1974) examined the percutaneous absorption of lindane dissolved in acetone and applied to the skin of human subject (n = 6). Radiolabeled lindane (4 μg/cm^2) was applied to ventral forearm skin and the urinary excretion of ^{14}C was measured for 5 days after the single topical application. The skin sites were not protected and subjects were asked not to wash the area for 24 hours. Data obtained after i.v. dosing was used to correct the skin penetration data for incomplete urinary recovery. Results indicate that 9.3% (SD 3.7) of the dose was absorbed.

Results from a more recent study, also with lindane dissolved in acetone and applied to the ventral forearm of human subjects, suggest that up to 20% of the dose may be absorbed in healthy adults (Dick et al., 1997). In this study, absorption was estimated using disappearance techniques. Lindane was applied to skin and covered with a nonocclusive patch. Six hours after application approximately 80% of the applied

lindane dose (120 mg lindane per ml acetone) had not been absorbed and 14% of the dose was found in the stratum corneum (measured by tape-stripping). The authors conclude that 5% of the applied dose was absorbed to the systemic circulation by 6 hours. By 24 hours, the stratum corneum contained very little of the applied lindane suggesting that all the lindane detected in the stratum corneum at 6 hours had been absorbed.

F.1.4.5.2 Selection of Absorption Value

A. Discussion

The data available on percutaneous absorption of lindane or other HCH isomers are limited. Much of the available data on dermal toxicity of HCH in humans is from cases in which lindane is dermally applied as a medicine to treat scabies. While we know from these studies that lindane in topical creams and lotions is efficiently absorbed through the skin (Ginsburg et al., 1977), it is not possible to quantify the amount of lindane to which these individuals were exposed or the percent of the dose that was absorbed (ATSDR, 1998). Furthermore, creams and lotions are not considered relevant vehicles for our purposes. It is difficult to predict how well data on dermal absorption from these vehicles approximates absorption of HCH bound in soil.

Only one study was located examining absorption of soil-bound lindane, and it was an *in vitro* experiment where absorption was quite low, less than 3% of the applied dose. In the human *in vivo* studies, absorption of lindane dissolved in acetone was estimated to be in the range of 10-20% of the applied dose. It is difficult to know how much of the applied dose in the Feldman and Maibach (1974) study was lost from the skin surface by washing, evaporation or the gradual exfoliation of outer layers of the stratum corneum. It is also difficult to predict how well data on lindane dissolved in acetone reflects absorption of the compound bound in soil.

B. Other Agency Recommended Default Values

The most recent CAPCOA guidelines recommend using 10% as the dermal absorption point estimate for hexachlorocyclohexane from soil (CAPCOA, 1993). This number is based on Clement Associates (1988) which suggests using a default of 10% for organic compounds when quantitative data are not available to estimate chemical-specific dermal absorption fractions from soil. Cal/EPA's Department of Toxic Substances Control (DTSC) currently recommends using 10% as the default dermal absorption factor for hexaclorocyclohexane, also based on Clement Associates (1988). In addition, U.S. EPA Region IX suggests 10% as the default point estimate (U.S. EPA, 1995b).

C. OEHHA Recommendation

Until further data are available (data on lindane or other hexachlorocyclohexane isomers that allows the determination of a chemical-specific number, or data on other organics suggesting a more appropriate default value for this class of chemicals),

OEHHA recommends adopting 10% as the default point estimate for dermal uptake of lindane and other hexachlorocyclohexanes from soil.

F.1.4.6 Dermal Absorption Fraction for Di(2-ethylhexyl)phthalate (DEHP)

Recommend point estimate for dermal uptake from soil – 10%

F.1.4.6.1 Studies Considered

A. Key Studies

No studies were located on dermal absorption of di(2-ethylhexyl)phthalate (DEHP) from soil.

The National Toxicology Program investigated the dermal absorption of ^{14}C-labeled DEHP in male F344 rats (Melnick et al., 1987). The labeled compound was dissolved in ethanol and applied directly to the skin (30 mg DEHP/kg body weight; n = 3 per time point). The ethanol was then evaporated and the site of application was covered with a perforated plastic cap. After five days, approximately 93-95% of the applied dose was recovered from the skin at the site of application and the plastic caps. Approximately 5% of the applied dose was recovered in urine and feces, while the amount of the label remaining in the body five days after dosing was less than 2 % of the applied dose of DEHP.

Ng et al. (1992) examined dermal absorption of several organic compounds in hairless guinea pigs, including DEHP. In an *in vivo* study, radiolabeled DEHP dissolved in acetone (53 μg DEHP; 34 nmols/cm^2) was applied topically on a dorsal area of the animals which was then covered with a nonocclusive patch. After 24 hours, the patch was removed and the dosing site cleaned to remove any unabsorbed compound. Absorption (estimated from urine and feces) was monitored up to 7 days post treatment. To account for incomplete excretion after the compound was absorbed, a dose of ^{14}C-DEHP was given intramuscularly to a group of animals (n=5) and radioactivity was measured in urine and feces for up to seven days. After 24 hours, 3% (7% after correction) of the dermally applied dose was eliminated in urine and feces. After seven days, approximately 21% (53% after correction) of the dose had been absorbed by the skin and eliminated. An additional group (n=6) of animals was given DEHP (53 μg) dermally. After 7 days, ^{14}C content (% of applied dose) was as follows: urine, 18 ± 4; feces, 4 ± 1; skin wash after 24 hrs, 32 ± 10; skin patch, 13 ± 5; skin (dosed area), 5 ± 3; other tissues (liver, fat, muscle, skin), 4 ± 3%. An additional 10% was estimated to be lost to volatilization.

In a more recent *in vivo* study, Chu et al. (1996) examined skin retention of solvent applied DEHP in hairless guinea pigs (n = 4/group). It was reported that 11% of the applied dose remained bound in the skin after 24 hours (applied dose = 119 μg/cm^2). Additional data from this study suggest migration of DEHP from the skin into the

systemic circulation, but the use of different applied doses at each time point of the study prevents an unequivocal conclusion. The authors also reported that the percent absorbed at 24 hours that was reported by Ng et al. (1992; summarized above) was higher than that found in this study, with nearly identical experimental protocols. They attributed this difference to the higher doses used in the present study (10 times higher when expressed in $\mu g/cm^2$) stating that saturation might have occurred at higher doses, resulting in a lower fractional absorption.

F.1.4.6.2 Selection of Absorption Value

A. Discussion

The data available on percutaneous absorption of DEHP are limited. No data were found on absorption in humans or absorption of the compound bound to soil. It has been suggested that the skin of rodents is more permeable than that of humans (Wester and Maibach, 1983) based on chemicals that did not include DEHP. It has also been suggested that the use of soap/water washes can alter dermal absorption, as was seen with benzo[a]pyrene. Moody et al. (1995) demonstrated a "wash in" phenomenon where soap and water washes aided the retention of benzo[a]pyrene in skin. Furthermore, it is difficult to predict how well data on dermal absorption from an aqueous solution approximates absorption of DEHP bound in soil. These factors all deserve further study.

Based on the data of Ng et al. (1992) and Chu et al. (1996), it appears that the absorption of DEHP is slightly less than that of benzo[a]pyrene. OEHHA is currently recommending a default value of 13 % for the absorption of benzo[a]pyrene from soil.

B. Other Agency Recommended Default Values

The most recent CAPCOA guidelines do not provide a recommended value for DEHP. Cal/EPA's Department of Toxic Substances Control (DTSC) currently recommends using 10% as the default dermal absorption factor for organics, including DEHP. This is based on Clement Associates (1988) which suggests using a default of 10% for organic compounds when quantitative data are not available to estimate chemical-specific dermal absorption fractions from soil. U.S. EPA Region IX suggests 10% as the default point estimate for DEHP (U.S. EPA, 1995b).

C. OEHHA Recommendation

Until further data are available (data on DEHP allowing determination of a chemical-specific number, or data on other organics suggesting a more appropriate default value for this class of chemicals), OEHHA recommends adopting 10% as the default point estimate for dermal uptake of DEHP from soil.

F.1.4.7 Dermal Absorption Fraction for 4,4' –methylenedianiline

Recommended point estimate for dermal uptake from soil: 10%

F.1.4.7.1 Studies Considered

A. Key Studies

Brunmark et al (1995) utilized a patch-test method to evaluate dermal exposure of and pharmacokinetics of 4,4'-methylene dianiline (MDA) dissolved in isopropanol. Measurements of MDA were made in plasma and urine of the five human volunteers. The extent of absoprtion was evaluated by measuring the amount remaining in the patch after 1 hour. The amount absorbed ranged from 25 to 29% under these conditions. The authors also describe elimination half-lives from plasma and urine.

Workers were monitored for two consecutive weeks in a fibre glass pipe factory for dermal exposure to MDA using both cotton glove and hand wash monitoring (Brouwer et al., 1998). Urinary excretion of methylene dianiline was also evaluated. Urinary MDA levels correlated well with exposure measurements. Geometric means of daily exposure ranged from 81 to 1783 μg MDA, while 24 hour urine samples ranged from 8 to 249 μg MDA. Given that Brunmark identified a urinary half-life of MDA of 7 hours and that the measurements on the hands and forearms of the workers correlated strongly (0.94) with the urinary excretion of MDA, one can roughly estimate that between 10 and 14% of the MDA on the hands and forearms was absorbed by the workers.

F.1.4.7.2 Selection of Absorption Value

A. Discussion

Both the Brunmark et al (1995) and the Brouwer et al (1998) papers indicate that MDA is absorbed across the skin. Brunmark report a median value of 28% absorption from an isopropanol solution under occluded conditions over an hour. It is difficult to relate this information to extent of absorption from soil which is likely to be less. Isopropanol itself may increase absorption relative to a soil matrix. However, it is clear that the compound can be absorbed to a significant extent from an isopropanol solution. Analysis of the Brouwer et al (1998) data indicates a rough estimate of absorption of 10 to 14 % under workplace exposure conditions where surface contamination with MDA was widespread. Thus, it appears that the default absorption value of 10% for organic compounds would be reasonable for absorption of MDA from soil.

B. Other Agency Defaults

While no specific values for methylene dianiline were located, both the Department of Toxics Substances Control and CAPCOA have utilized default values of 10% absorption from soil for nonionized organic compounds.

C. OEHHA Recommendation

Until further data are available describing absorption of MDA from soil, OEHHA recommends the default value of 10% for organics. This is consistent with the information in Brouwer et al. (1998).

Table F.1 Point Estimate And Default Dermal Absorption Factors (ABS) As Percent Of Selected Chemicals From Soil

CHEMICAL	ABS (percent)	REFERENCE
Inorganic chemicals		
Arsenic	4	Wester et al., 1993b
Beryllium	1	default (Clement, 1988)
Cadmium	0.1	Wester et al., 1992a
Chromium (VI)	1	default (Clement, 1988)
Lead	1	default (Clement, 1988)
Mercury	10	default (this document)
Nickel	4	Fullerton et al. 1986
Organic chemicals		
Di(2-ethylhexyl)phthalate	10	Default (Clement, 1988)
Hexachlorocyclohexanes	10	Default (Clement, 1988)
4,4'methylene dianiline	10	Default (Clement, 1988); Brouwer et al, 1995
Polychlorinated biphenyls	14	Wester et al., 1993a
Polychlorinated dibenzo-p-dioxins and dibenzofurans	2	Shu et al., 1988
Polycyclic aromatic hydrocarbons (as BaP)	13	Wester et al., 1990

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